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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,574	04/23/2001	Marston Manthorpe	1530.0180002/EKS/EJH	1437

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/839,574	MANTHORPE
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 23, 2002*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *310-357* is/are pending in the application.

4a) Of the above, claim(s) *312, 315-325, 327, 335, 337, 338, 344-346, 350,* 353-357 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *310, 311, 313, 314, 326, 328-334, 336, 339-343, 347-349, 351, and* 352 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Aug 17, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13-15*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 12 on 12/23/02.

Claims 1, 58, 10, and 164-309 were canceled as requested.

Claims 310-357 were added.

Information disclosure statements were received and entered as Paper Nos. 13 and 14 on 12/23/02.

An IDS was received by FAX on 6/13/02, and was entered as Paper No. 15. This IDS listed copending Application 09/557, 907 which was considered. However, the form 1449 was not initialed for this reference in order to avoid publication of the application number in the event allowable subject matter is found herein.

Previously, in Paper No. 8, Applicant elected for examination the species of invention comprising sodium bicarbonate, influenza nucleoprotein, cationic lipids, Pluronic R 25R2, and intramuscular administration. Claims limited to the species of auxiliary agent, Pluronic R 25R2, were found to be novel and non-obvious over the prior art. In accordance with MPEP 803.02, the Office extended the search to a second species of auxiliary agent, *i.e.* Tween 80. Claims reciting this species were found to be obvious over the prior art. By amendment in Paper No. 12, Applicant deleted Tween 80 from the claims. Accordingly the Office now selects another species of auxiliary agent from the originally available species disclosed in the invention, i.e. Pluronic F63. Claims 310, 311, 313, 314, 326, 328-334, 336, 339-343, 347-349, 351, and 352 read on the elected invention. Claims 312, 315-325, 327, 335, 337, 338, 344-346, 350, and 353-357 are

withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claims 310, 311, 313, 314, 326, 328-334, 336, 339-343, 347-349, 351, and 352 are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 310, 311, 313, 314, 326, 328-334, 336, 339-343, 347-349, 351, and 352 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 310, 311, 313, 314, 326, 328-334, 336, 339-343, 347-349, 351, and 352 are indefinite because the metes and bounds of "essentially free of chloride anion" are unclear. Applicant indicates at page 24 of the response that this phrase is defined in the specification at page 31 paragraph [0083] which states the "phase "essentially free of chloride ion" indicates that no source of chloride ion is intentionally added to the composition other than as an incidental but integral part of another reagent being added to the solution." However, the definition in this passage is itself indefinite. It is unclear what is an "incidental but integral part of another solution", and it is unclear how much chloride ion can be added in this fashion. For example, if a

cationic lipid is added to the composition and the cationic lipid contains sufficient NaCl to render the composition 50 mM in chloride ion, is this within the scope of the claimed invention? In the end, the process by which the composition of the claims is made is immaterial, and what matters is the amount of chloride ion allowed to be in the composition. The claims fail to make clear what is this amount.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 310, 311, 313, 314, 326, 328-334, 336, 339-343, 347-349, 351, and 352 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (US Patent 6,120,794) in view of Ulmer, Science 259: 1745-1749 (1993), Wheeler et al (US Patent 5,861,397, Gregoriadis (FEBS LETT 402(3): 107-110, 199)), Ishii et al (AIDS Res. Hum. Retrovir. 13(16): 1421-1428, 1997), and Hartikka et al (Gene therapy 7(14): 1171-1182, 7/2000).

The claims are directed to methods of delivering influenza nucleoprotein to a vertebrate by intramuscularly administering a composition comprising about 1 to about 30 mg of a polynucleotide in aqueous solution encoding a polypeptide, wherein the aqueous solution

comprises about 50 to about 250 mM of sodium bicarbonate, and wherein the composition also comprises Pluronic F63. The aqueous solution must be essentially free of chloride ion, and the influenza nucleoprotein must be expressed in a detectable amount. The composition also comprises a cationic lipid.

Liu teaches nucleic acid compositions and methods for delivering them to vertebrate cells in vivo. See abstract. The composition may comprise e.g. an aqueous solution with 100 micrograms of plasmid DNA encoding a polypeptide. See column 10, lines 21-25; column 21, lines 30-38; and claim 1. The nucleic acid may also be mRNA. See column 9, lines 37-59, especially line 39. The composition may be buffered with bicarbonate, and may contain saline (150 mM NaCl). See column 8, lines 62-66. The composition comprises cationic lipids, including any cationic lipid which is effective for use in liposomes or for producing lipid complexes capable of delivering biologically active material to cells. See e.g. paragraph bridging columns 5 and 6. A colipid may be included, and the ratio of colipid to cationic lipid may be within the range of 2:1 to 1:2. See e.g. Table 1 at column 13. The composition may comprise the surfactant Pluronic F63. See column 7, lines 33 and 55; and Tables 1-4. Delivery may be intramuscular. See column 11, lines 24-32, especially line 27; and see claim 19. The composition may comprise a colipid, particularly DOPE. See column 7, lines 56-67, and Tables 1-4.

Liu does not teach a nucleic acid encoding influenza nucleoprotein, or an aqueous solution essentially free of chloride ion. Liu is silent as to the concentration of bicarbonate in the composition, and as to the nature of the muscle into which the composition should be delivered.

Ulmer teaches a method of inducing a protective immune response in a mouse by quadriceps injection of naked DNA comprising an expression cassette encoding influenza nucleoprotein. See entire document, especially abstract, and page 1746, column 2, lines 15-20..

Wheeler teaches a compositions and methods for nucleic acid-mediated vaccination comprising 28 mM sodium bicarbonate. Wheeler also teaches that cationic liposomes are useful for delivering nucleic acids to cells in vivo. See *e.g.* column 2, line 60 to column 3, line 3; column 7, lines 32-35; and column 14, lines 22-53.

Gregoriadis teaches that immunization by intramuscular injection of nucleic acids encoding antigens can be improved by us of cationic liposomes. See abstract. Gregoriadis teaches injection into skeletal muscle of the hind leg. See page 107, column 2, lines 1-5 of third full paragraph.

Ishii teaches that cationic liposomes are a strong adjuvant for DNA immunization. See title and abstract.

Hartikka teaches a method of expressing influenza nucleoprotein *in vivo* by intramuscular injection of plasmid DNA. Hartikka teaches that expression can be improved if 150 mM sodium phosphate is substituted for the 150-154 mM NaCl which is frequently used by those of skill in the art. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method and micellar complexes of Liu to deliver to skeletal muscle the influenza nucleoprotein expression vector of Ulmer. First, one would have been motivated to modify the method of Ulmer by using cationic liposomes as a delivery vehicle, because Gregoriadis and Ishii

teach that the use of cationic liposomes constitutes an improvement over naked DNA delivery. Then one would have been motivated to substitute the method and micellar complexes of Liu for those of Gregoriadis or Ishii because Liu teaches that the disclosed micellar complexes are stable, whereas stability is a major problem limiting the use of liposomes. See column 1, lines 8-13, 32-36, and 49-51. Liu is silent as to which salt of bicarbonate is used in the method, and as to the concentration of bicarbonate. However, one of ordinary skill in the art seeking guidance as to which salt to use, and in what concentration, would have looked to Wheeler who teaches that the delivery of nucleic acid/cationic lipid compositions may be carried out in solutions comprising 28 mM bicarbonate (2.4 g Na bicarbonate/L). See column 13, lines 38-48.

It would have been similarly obvious to substitute the 150 mM sodium phosphate of Hartikka for the 150 mM sodium chloride of Liu. One would have been motivated to do so in order to improve the amount of polypeptide expression obtained in the method, as taught by Hartikka. This would result in an aqueous solution that is essentially free of chloride ion.

It is noted that the claims require a sodium bicarbonate concentration of about 50 to about 250 mM. Although none of the cited references teaches sodium bicarbonate of this concentration, generally differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. See MPEP 2144.05(b). In this case, the concentrations in question are clearly not critical for the practice of the invention because the specification teaches that a broader concentration will function. See page 28, paragraph 75, which teaches that as little as 25 mM sodium bicarbonate

may be used in the invention. The cited art is combined to teach the general conditions of the claims, i.e. a composition "about" 50 mM sodium bicarbonate. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments filed 12/23/02 have been fully considered but they are not persuasive.

The portion of Applicant's arguments pertinent to the rejection above is presented at pages 29-30, of the response. Applicant notes that Liu teaches a composition comprising Pluronic F63, but asserts that this composition is not essentially free of NaCl as required by the instant claims, but comprises 150 mM NaCl. This argument is unpersuasive because it does not take into account the teachings of Hartikka, who shows that in vivo expression of influenza nucleoprotein by intramuscular injection of plasmid DNA can be improved if 150 mM sodium phosphate is substituted for the 150 mM NaCl. This would result in a composition that is essentially free of NaCl.

Applicant further argues that the sodium bicarbonate concentration taught by Wheeler does not render obvious theinstnat invention becasue it is outside the range recited inthe claims.

This is unpersuasive forthe reasons set forth in the rejection. MPEP 2144.05(b) indicates that generally differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that this concentration is critical. In this case, the concentrations in question are clearly not critical for the practice of the invention because the specification teaches that a broader concentration will function. See page 28, paragraph 75, which teaches that as little as 25 mM sodium bicarbonate may be used in the invention. The cited art is combined to teach the general conditions of the claims, i.e. a composition "about" 50 mM sodium bicarbonate. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to

the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JEFFREY SIEW
PRIMARY EXAMINER
3/1/05